

Research Article

MDSCs IN COVID-19 Why should we care?

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For the last few months, we all, scientists and industry alike, have been working in a rush to try to understand the mechanics of the SARS-CoV2 coronavirus, the cause of the Covid-19 disease. Efforts have been particularly centered on finding ways to predict the bad clinical evolution that sometimes occur in patients with minimal respiratory symptoms at presentation. We know already that most of these patients do not progress to more severe forms of the disease. There is however a small percentage of patients that develop what is called Severe Acute Respiratory Syndrome or SARS, which is the cause of death in this disease.

SARS (or more generally speaking ARDS) is caused by a massive unordered reaction of the immune system in the lungs. We have found some data in the recent literature indicating the presence of a type of cells called Myeloid Derived Suppressor Cells (MDSCs) over the course of the disease. These cells have been previously studied for their major role in nurturing cancer growth. After a careful review of the literature, now we believe that MDSCs may also have a major role in SARS progression and, in the survivors, they could be responsible for post-Covid-19 health conditions long time after recovery from the acute phase of the disease. If our premises are confirmed, we think that these cells should be priority targets for the design of predictive methods based on their early detection and quantitation. MDSCs should also be the focus of investigation in search for candidate drugs that could inhibit their development in the bone marrow, their migration into the lungs, or their suppressive regulation of T cell activity during the viral infection and beyond.

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Introduction

Since the first cases of pneumonia were diagnosed in Wuhan, China, in Dec 2019^{[1][2][3]}, the new SARS-CoV2 coronavirus has taken hold of the entire world in the form of a pandemic with hundreds of thousands deaths and, specially, the growing uncertainty associated with the absence of an end in sight to it. Despite all this, the Covid-19 disease has also brought positives amongst all the havoc. A case in point: both the scientific community and the industry are joining forces in an almost unprecedented approach to work together for the common goal of being able to stop the death count.

In our view, this common front should aim at rapidly improving, at least, three main aspects of the disease: 1) The early detection of patients at risk of developing SARS, 2) The early treatment to prevent lethality 3) The appraisal of the post-recovery long-term health consequences in survivors.

As we will discuss in the coming pages, the key for a successful strategy against the Covid-19 disease consists in developing tools (both diagnostic and therapeutic) that can be deployed during the very early phases of the disease. With this, we refer to the first flu-like symptoms of the disease. When these first symptoms are present in people at risk of developing SARS (elderly people or patients with previous conditions such as hypertension, diabetes, ischemic heart disease, cancer or COPD^[4]), we should be able to detect early signs of deterioration and, consequently, apply the according therapeutic measures to prevent further worsening. In this regard, we have already proposed a treatment for this budding phase of the disease. The treatment consists in an adaptation of the scheduled inhalers used in the chronic treatment of asthma and this approach is predicted to slow down or stop the progression of the disease in this group of patients at risk^[5].

The early phases of the Covid-19 disease are usually spotted at home, at a primary care center or at the hospital ER, where patients look for a first health assessment of their symptoms (cough, diarrhea, abdominal discomfort, chest tightness, dysgeusia, etc.). At this point, we would like to be able to decide if a patient is really at risk of quickly progressing towards a more severe form and in this case, he/she should be transferred to the ward or referred to the closest hospital for further evaluation and treatment, or, if, on the contrary, we could wait to take further measures.

To sum up, we are in serious need of appropriate tools to precisely assess on the spot the risk of developing the severe complications in suspected or confirmed Covid-19 patients .

Covid-19 Disease

The Covid-19 disease as we know it is in fact two diseases in one. Most of the people infected by the SARS-CoV2 coronavirus are either asymptomatic throughout the entire course of the disease or have more or less mild symptoms followed by an apparently full recovery^[6]. In those patients, the infection behaves more or less like a classical respiratory viral illness. In a minority of infected people, however (around 10%), the symptoms (particularly the respiratory symptoms) are more severe and, thus, the disease can evolve into what is called an Acute Respiratory Distress Syndrome (ARDS or SARS). ARDS is often an irreversible process that can lead to death (most deaths following Covid-19 are due to ARDS) or, in survivors, to long term yet uncharacterized chronic health conditions^[7].

The scientific community has reached a consensus with respect to the underlying major mechanism of the disease. It appears that the cause of the sudden clinical deterioration that occurs in a minority of patients with Covid-19 is due to an overreaction of the immune system within the lungs in the form of a so-called “cytokine storm”^{[8][9]}. This aberrant reaction is most likely due to the uncontrolled response of the pulmonary innate immune system to the CoV2 coronavirus infection^{[10][11]}. On the one hand, on the march leading to ARDS, there is an overabundance of pro-inflammatory cytokines that flood into the lungs and, on the other hand, there is a striking absence of the major control component of the immune system: T cells. These cells in all of their forms and shapes (CD4+ Helper, CD8+ Cytotoxic, Tregs or NK cells) are either dramatically reduced, exhausted, or inactive in the context of ARDS (and this is often translated into a global overall sharp decrease in lymphocyte count in the peripheral blood of these patients^[12]). In other words, they are unable to orchestrate an ordered sequential adaptive immune response to the coronavirus infection. Instead, during the early phases of ARDS, we witness a runaway chain reaction of the immune system with a plethora of pro-inflammatory cytokines and chemokines, that either destroy the lung tissue (leading to liquid occupance of the alveoli) or attract effector cells like monocytes or neutrophils with similar destructive power.

Main

One of the reasons behind the apparent inaction of the adaptive immune system (mainly T and B cells) is the SARS-CoV2 virus itself. The genome of this virus encodes several proteins that have precisely this function (to anesthetize the adaptive immune system by blocking for instance the type I interferon response^[13]). Another reason, and the one that is most relevant to this paper, is linked to

the kind of cells that, coming from the Bone Marrow, are attracted to the site of the infection in the alveolar and perialveolar lung space.

Cells that are attracted to the lungs during SARS are mainly monocytes (the precursors of non-resident macrophages as well as of dendritic cells) and granulocytes (PMN). But, as we will see, not any type of monocytes or granulocytes.

Classical monocytes are characterized by a pattern of expression of surface proteins ($CD14^{hi}CD16^{-}$) that facilitate their purification by flow cytometry^[14]. During SARS however it has been shown that there is a sharp decrease in this subpopulation of classical monocytes and instead atypical monocytes with the signature $CD14^{low}HLADR^{low}CD16^{hi}$ are abundantly present in the peripheral blood. Moreover, this population can be accurately quantified and it positively correlates with disease severity (i.e. high prognostic value)^[15].

Also in the lungs of patients with Covid-19, a subpopulation of atypical neutrophils, the so-called Low Density Granulocytes (LDG), has been identified and are likely to have a decisive function in the fate of the disease^[16].

Indeed, low density granulocytes have been recently identified in patients with Chronic Critical Illness (CCI), 'a persistent inflammatory-immunosuppressive and catabolic syndrome'^[17]. They are also overrepresented during septic shock and here their presence is directly correlated with bad prognosis^[18].

Myeloid Derived Suppressor Cells (MDSCs)

These atypical forms of myeloid cells have been recently grouped together with other types of peripheral mononuclear cells under the provisional classificatory umbrella of Myeloid Derived Suppressor Cells or MDSC^[19]. MDSCs are defined as immature myeloid cells that egress from the bone marrow in different disease contexts. What all these cells have in common is their capacity to suppress the adaptive immune system^[20]. Indeed, MDSCs inhibit adaptive antitumor immunity by inhibiting T cell activation and function (T-cell receptor downregulation, T-cell cycle inhibition and immune checkpoint blockade)^[21], and by driving and recruiting T regulatory cells. Immunosuppression by MDSCs is also mediated by the generation of reactive oxygen species (ROS)^[22] and cytokine release (IL-10, TGF- β)^[23].

Two different subtypes of MDSCs, monocytic MDSCs and granulocytic MDSCs (mMDSCs and gMDSCs), have been identified^[24] and the expansion and activation of MDSCs have been shown to be triggered by a number of cell-derived factors. For instance, granulocyte-colony-stimulating factor (G-CSF) has been identified as a major factor for the differentiation of gMDSCs^[25], and granulocyte-macrophage colony-stimulating factor (GM-CSF) has been shown to play a key role in mMDSC production^[26].

Sure enough, both G-CSF and GM-CSF are among the cytokines that are produced in excess in the lungs of SARS patients, implying that they are probably the necessary cues for the differentiation of both M and G-MDSC and their migration from the bone marrow into the inflamed lungs^{[27][28]}. Not less important, a major chemoattractant for neutrophils (the CXCL-8 chemokine) is also one of the higher expressing cytokines during SARS^[29] and most of the chemokines known to attract monocytes are produced in abundance in the lungs of Covid-19 patients. All of these factors are exceedingly spilled out of the lungs into the circulation^[30]. In a nutshell, the prerequisites for the production of MDSC and their massive migration into the lungs are clearly fulfilled by the cytokine storm taking place within the lungs of these patients.

MDSCs have been thoroughly characterized in several autoimmune diseases like SLE^[31], DMI^[32], in severe sepsis^[33], where their prominence is linked to disease severity, as well as in different tumor models, where they are consistently involved in promoting tumor growth^[34].

This latter aspect has a potential important bearing on Covid-19. Indeed, cancer has been consistently placed along the list of health preconditions with higher risk of developing SARS^[35] [36]. More specifically, the elevated risk of death is correlated with active cancer and not with its current treatment at the time of contracting Covid-19^{[37][38]}. As we know, active cancer is precisely when MDSC are at their peak both in terms of number and functional activation^[39].

Particularly relevant is also the role of MDSC in a plethora of viral infections^[40]. For instance, during infection with the HCV (A +ssRNA virus like the CoV2 coronavirus), CD4+, CD8+ and NK cell functions are abrogated by a prominent population of MDSC, thus promoting viral replication and disease chronicity^{[41][42]}. Also M-MDSC with immunosuppressive activity have been isolated from the blood of humans and mice infected with another RNA virus (the influenza A virus or IAV)^[43]. Finally, the effect of both G-MDSC and M-MDSC on anti-viral immunity has been amply studied in HIV infected patients and animal models, showing that mechanisms of immune-suppression can be attributed to

inducible NO synthase (iNOS), Arginase-1 (Arg-1), or the generation of Reactive Oxygen Species (ROS) by associated MDSCs^{[44][45]}.

Importantly, and paradoxically, MDSC (both G and M-MDSC) show strong features of proinflammatory cells. In fact, upon activation, they can injure endothelial cells and release a large quantity of tumor necrosis factors (TNFs) and type I and type II interferons (IFNs)^[46]. In the case of neutrophils, this effect has been linked to an excess of so-called neutrophil extracellular traps (NETs) that are released from neutrophils during inflammation. NETs are webs of extracellular DNA decorated with histones, myeloperoxidase, and elastase^[47]. Although NETs contribute to pathogen clearance, excessive NET formation, as observed after massive tissue damage, promotes inflammation and tissue damage in sepsis as well as in macroscopic tissue injury^[48]. NETs have been extensively studied in the context of postinflammatory thrombosis as observed in the Covid-19 disease^[49] and the contribution of NETs to coagulation and platelet aggregation (and the elevation of molecular markers like the D-Dimer) has been extensively studied^[50]. Therefore, the importance of NETs in SARS cannot be ignored anymore, to the point that it has been recently postulated that their abundance could be intimately correlated with the clinical deterioration seen with Covid-19^[51]. Since NETs are the consequence of both tissue damage and the presence of proinflammatory neutrophils such as the LDG as present in SARS, we foresee that the framework of this paper could also be applied to predict the occurrence of pro-coagulation events such as the thrombosis and ischemic heart and brain complications that are often observed in the severe course of the disease.

Long term effects of immunosuppression by MDSC

A very prominent aspect, and also a very important one for this layout, is the long term effects of MDSC. It has been extensively reported that the appearance of MDSC is not an isolated/reversible event. Indeed, After Severe Sepsis/Septic Shock in humans, circulating MDSCs are persistently increased, functionally immunosuppressive, and associated with adverse outcomes^[52]. This long term phenomenon has also been reported in rat models after Trauma and Hemorrhagic Shock^[53]. The phenomenon is so important that the term sepsis-acquired immunodeficiency has been recently coined^[54]. There is now increasing evidence that acquired immune dysfunctions might contribute to the increased susceptibility to secondary infections or autoimmune disorders in the wake of recovery after a long ICU stay^[55]. That there is a permanent modification after sepsis, has been demonstrated using a molecular approach and it has been linked to specific epigenetic changes^[56]. There are even

candidate drugs like LDK378 (an inhibitor of the ALK kinase) that prevents the recruitment of MDSCs to spleen via the CCR2 pathway in mice with sepsis^[57].

To our knowledge, a similar long-term immunosuppression after recovery from viral infections has not been reported yet. We attribute the absence of studies of this kind to the fact that the interest in these cells in relation with acute or chronic viral infections is only very young (perhaps limited to the last three years). This lack of data, particularly in the Covid-19 context, should encourage scientists around the world to delve into the issue. That will help us all to better understand the disease and, perhaps, to come up with new urgently needed solutions therefor.

To recapitulate, there are some experimental observations that indicate the presence of MDSC in the lung (the epicenter of SARS) of Covid-19 patients. We believe that these cells may have a pivotal role in the unordered immune response that is at the core of SARS. We predict that the presence of MDSCs will be relevant even after recovery from the acute disease and could be cause of yet unknown chronic health conditions post-Covid-19. We finally believe that the MDSC cells should be analyzed and characterized in the Covid-19 disease, and we foresee a plethora of new insights, diagnostics and treatments that will come out of such endeavor.

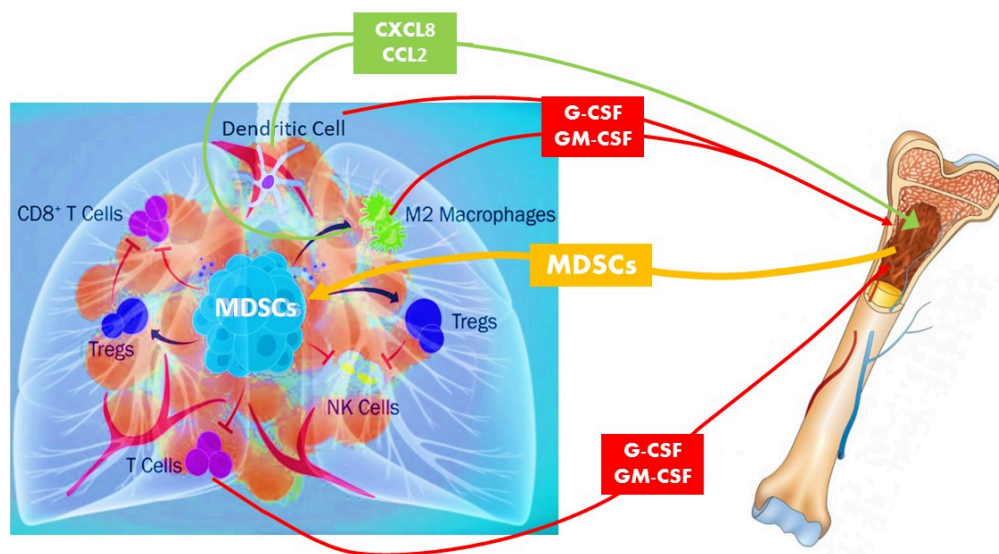


Figure 1

Adapted from <https://www.rndsystems.com/>

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